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The Acute Toxicity of Tannic Acid Administered Intragastrically

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ABSTRACT

The LD_{50} ± S.E. of tannic acid given orally to albino rats was found to be 2.26±0.083 g. per kg. body weight, which is higher than its apparent LD_{50} when given per rectum. The immediate cause of death was respiratory failure preceded by convulsions when death occurred early and by hypothermic cachexia when death was delayed. Death was associated with a progressively developing hepatic necrosis and nephritis and a temporary acute gastroenteritis. It was accompanied by loss of weight and edema in many organs, evidence of stimulation of the spleen, adrenal cortex and testes, and atrophy of the thymus. Recovery in survivors was associated with a temporary increase in weight of the spleen and testes and persistence of loss of weight in the adrenal, pyloric stomach, and skin.

SOMMAIRE

La DL_{50} ± E.S. de l'acide tnnique donné par voie buccale à des rats albinos a été de 2.26±0.083 g. par kilo de poids corporel, qui est un chiffre plus élevé que sa DL_{50} apparente par voie rectale. La cause immédiate de la mort était un arrêt respiratoire, précédé de convulsions quand la mort se produisait précocement, et de cachexie hypothermique quand la mort survenait tardivement. On constatait aussi à la nécropsie une néphrite et une gastro-entérite temporairement aiguë. Ces pathologies s'accompagnaient de perte de poids et d'oedème au niveau de nombreux organes, des signes de stimulation splénique, du cortex surrénal et des testicules et une atrophie du thymus. La guérison chez les survivants s'accompagnait d'une augmentation temporaire du poids de la rate et des testicules et d'une diminution pondérale persistante des surrénales, du pylore gastrique et de la peau.

THE project herein reported was designed to obtain toxicity data basic to an estimate of the safe dosage limits of tannic acid added to barium sulfate formulations for use in diagnostic radiology. Lucke, Hodge and Patt[1] have recently reported, in this Journal, fatal liver necrosis in which tannic acid, contained in a barium sulfate diagnostic enema, was the only known causative agent. Similar cases have been reported from the United States of America,[2] and this led to a hearing for withdrawal of approval of one such tannic acid formulation by the U.S. Food and Drug Administration.[3] The situation confronting radiologists, who have used tannic acid since 1946 to improve the contrast in barium sulfate diagnostic enemas, has been reviewed.[4, 5] As tannic acid has been added to an estimated 600,000 barium sulfate enemas per year in the United States,[4] apparently without toxic effects, solution of the problem would appear to be related to determination of the dosage range of tannic acid which will, and which will not, produce toxic effects.

From preliminary observations in this laboratory,[6] the LD_{50} of tannic acid (Fisher Certified), given per rectum to albino rats with evacuation prevented, will be of the order of 1 g. or less per kg. body weight. As might be expected, the LD_{50} is considerably higher if rectal evacuation is permitted after two minutes, as in the usual radiological diagnostic procedure.[7] Pending solution of problems involved in rectal administration to animals and since the tannic acid–barium sulfate enema passes into the small bowel in up to 90% of patients given the preparation per rectum,[5] it was decided to measure the LD_{50} of tannic acid given intragastrically to albino rats. The drug is not vomited in this species and passes quickly into the small bowel. An estimate of the toxicity of tannic acid given intragastrically, therefore, provides an estimate of the toxicity of doses absorbed from the small bowel, which absorption must occur to varying degrees when the drug is added to a diagnostic barium sulfate enema. Since rectal administration is not commonly used in estimates of lethal doses of drugs, it was desired to obtain information on oral administration for purposes of comparison.

Most published data on toxic doses of tannic acid date back to the period 1925 to 1945 when the drug was extensively used in the treatment of burns and when its hepatotoxicity in man was discovered. At that time, based upon such evidence as the failure to produce liver necrosis in rats fed diets containing 1% or 2% tannic acid,[8] it was considered that this substance was poorly absorbed when given by mouth and a parenteral route of

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administration was employed in most experimental toxicity studies. From one report,[9] however, an approximation of the LD_{50} following oral administration in mice may be calculated at some 3.5 g. per kg. body weight, and rats were reported to be more resistant than mice.[9] Doses in the range of 2 to 8 g. per kg. were therefore selected for a pilot study from the results of which it was possible to select definitive doses for determination of the LD_{50} and the associated clinical and pathological signs of intoxication.

METHODS

Young male albino rats of a Wistar strain (CBL-W), weighing 125 to 200 g., were used. The animals were fed Purina laboratory chow and water *ad libitum*. For measurement of toxicity they were placed in metabolism cages, one rat per cage. To empty the stomach, food was withdrawn for 16 hours (overnight) prior to drug administration. Tannic acid was freshly dissolved in distilled water and given by intragastric cannula in a volume of 20 ml. per kg. body weight. The animal was then returned to its cage, which contained known amounts of chow and water, and was observed daily for five days. It was then put in the animal colony and observed casually for one month. Clinical measurements and observations were as listed below and as previously described in this Journal.[10]

Complete autopsies were performed on 15 to 17 rats which died, and where autopsy could be carried out within one hour of death to avoid the postmortem shifts reported by Boyd and Knight;[11] upon groups of 15 to 17 survivors at each of two weeks and one month; and upon the same number of controls, given no tannic acid, at each of these three intervals. At autopsy the wet and dry weights and the gross and microscopic appearance of the organs listed below were recorded. For microscopic examination, sections were stained with hematoxylin-phloxine-saffron. In addition, gross and, where indicated, microscopic pathology were recorded upon all other rats which died.

Tannic acid was used in the form of Fisher Certified Tannic Acid, which has the formula $3,4,5,\text{-}(OH)_3\ C_6H_2\text{-}COOC_6H_2\text{-}5\text{-}COOH\text{-}2,3\text{-}(OH)_2$. Following a pilot test on a range of doses from 2 to 8 g. per kg. body weight, the following doses were selected for definitive study on 16 to 42 rats per dose: 0.00, 2.00, 2.10, 2.15, 2.20, 2.40, 2.50, and 4.50 g. per kg. Statistical methods employed were those of Croxton.[12]

RESULTS

The $LD_{50} \pm$ S.E. was calculated to be 2.26 $\pm$ 0.083 g. per kg. The interval from administration to death was shorter the greater the dose of tannic acid. The mean interval from administration to death has been plotted against the dose producing death (Fig. 1). The regression was logarithmic and fitted best by the estimating equation shown in Fig. 1. At the LD_{50} the mean interval to death was 38 hours, and at lower doses the interval was prolonged to four to five days.

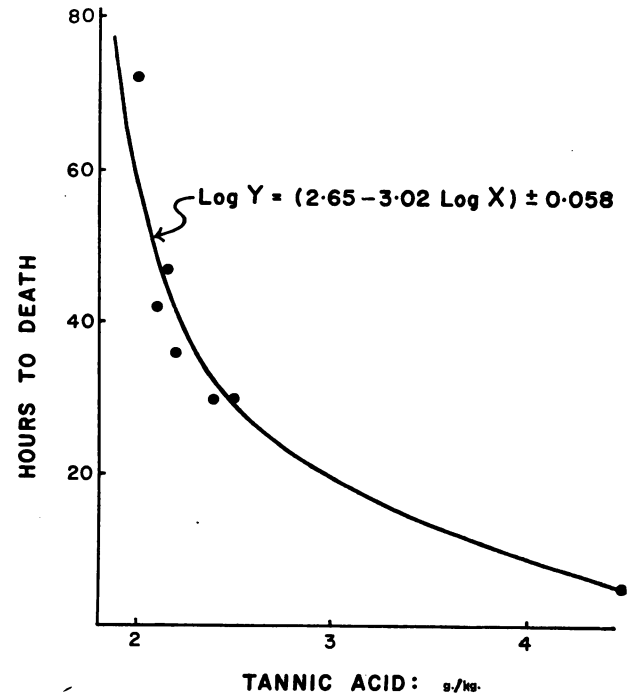

Fig. 1.—The regression on dose of tannic acid of mean interval to death.

The most common signs of intoxication were drowsiness, pallor, cyanosis, and diarrhea. These were assessed as 1+ to 3+, and a summary of mean values is shown in Fig. 2. Drowsiness and pallor reached a peak five hours after administration of lethal doses and continued at or somewhat below the peak for four to five days. Diarrhea and soft stools appeared during the first five hours and were absent at and after 24 hours. A slight to moderate degree of cyanosis appeared within one to two hours and persisted to four to five days. All of these signs were dose-dependent, i.e. they were more marked the greater the dose of tannic acid. A few animals exhibited cataleptic stances,

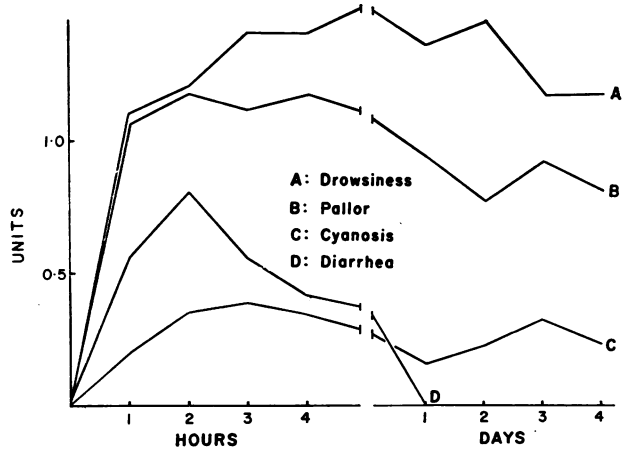

Fig. 2.—Shifts in the mean degree of drowsiness, pallor, cyanosis, and diarrhea following oral administration of tannic acid in the range of the median lethal dose.

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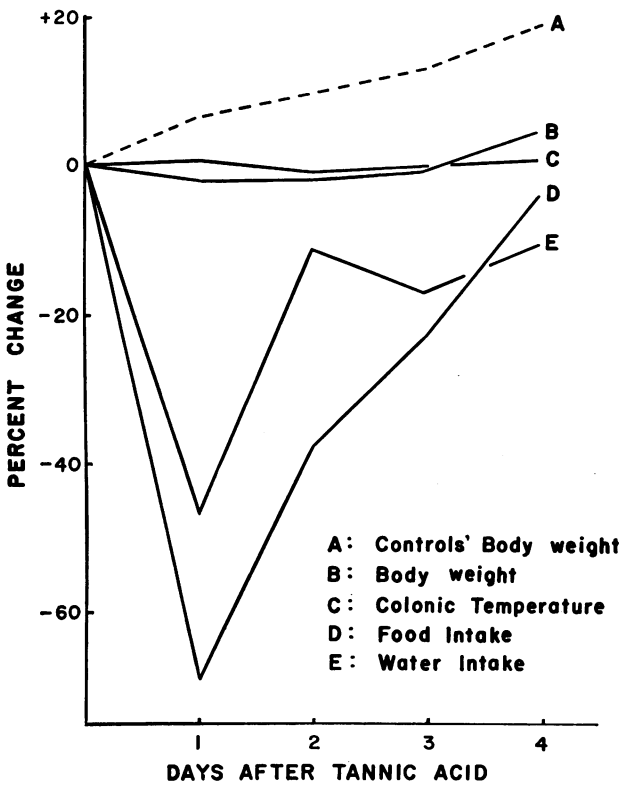

Fig. 3.—Percentage changes, from the day before administration of tannic acid, in body weight, colonic temperature (no significant change), food intake and water intake.

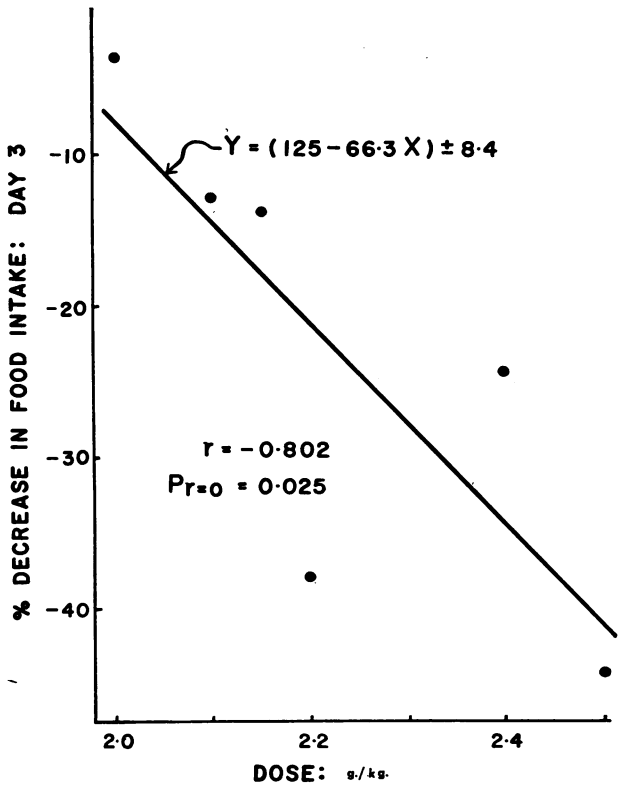

Fig. 4.—The regression, on dose of tannic acid, of % decrease from controls in food intake during the third 24-hour period.

in which the animal usually remained motionless for some time in an upright position on its haunches. A few went through apparently meaningless circular movements.

Along with these signs the animals had marked anorexia which reached a peak during the first day and disappeared in survivors during the fourth day. As a result, growth was inhibited, as shown in Fig. 3. Water intake was reduced but not to the same relative extent as food intake, which suggests that tannic acid produced a degree of thirst which partially overcame the oligodipsia due to reduced food intake. There were no significant shifts in colonic temperature during this period. Values for food intake, water intake, and colonic temperature in the control rats have not been shown in Fig. 3 because they did not change significantly over the interval studied.

A dose-response relationship existed for inhibition of growth and of food intake and water intake. An example of this relationship is shown in Fig. 4 in which the percentage decrease, from the day before drug administration, in food intake has been plotted against the dosage for one day, day 3 having been selected for this purpose. The regression shown in Fig. 4 could be fitted by the estimating equation, $Y = (91 - 330 \log X) \pm 8.5$, equally well as by the equation for linear regression shown in this figure.

A summary of statistically significant changes in the urine is illustrated in Fig. 5. Administration of tannic acid was followed by a dose-dependent diuresis which reached its peak during the second 24-hour period when the urine volume averaged

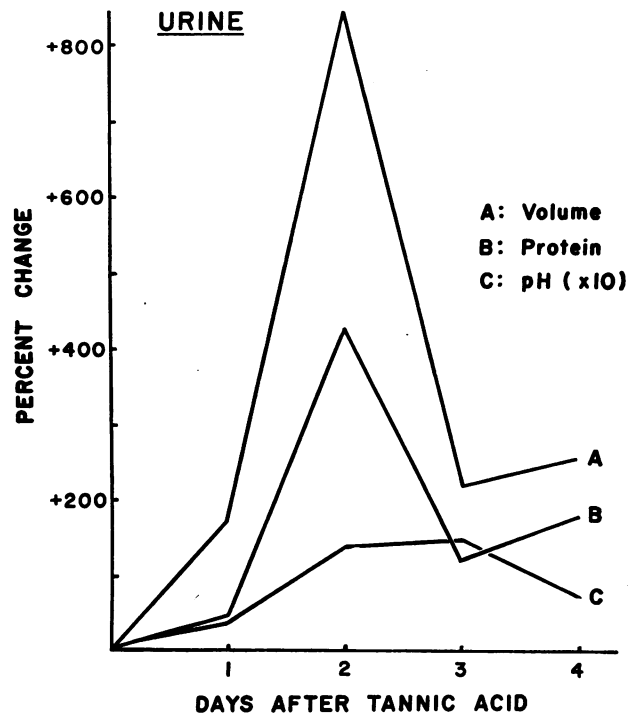

Fig. 5.—Percentage changes, from the day before administration of tannic acid, in urinary volume (calculated as ml. per kg. body weight per 24 hours), urinary protein excretion (calculated as mg. per kg. body weight per 24 hours), and urinary pH (shown for clarity as 10 times the actual recorded percentage changes).

TABLE I.—SHIFTS IN THE FRESH WEIGHT OF ORGANS AT AUTOPSY IN ANIMALS WHICH DIED AND IN SURVIVORS AT ONE FORTNIGHT AND AT ONE MONTH AFTER DRUG ADMINISTRATION†

Organ	*At death*	*Fortnight survivors*	*Month survivors*
Adrenal glands	+41.2**	−11.4	−20.5**
Brain	− 1.1	+ 7.1	− 5.7
Gastrointestinal tract:			
Cardiac stomach	+ 4.2	− 4.9	− 0.3
Pyloric stomach	− 3.9	− 4.2	−11.7**
Small bowel	−18.7**	− 1.0	− 3.5
Cecum	−22.4**	+ 5.0	+ 2.0
Colon	−15.3**	−11.1*	+ 6.0
Heart	− 2.9	+ 7.5	+10.7
Kidneys	−13.4*	+ 2.6	+ 5.9
Liver	−21.3**	− 9.9*	+ 1.9
Lungs	+22.1	+ 3.3	+15.6
Muscle (abdomen wall)	−13.2	− 3.2	−14.8
Salivary glands (submaxillary)	+ 1.1	+ 4.8	0.0
Skin	−13.4*	−11.4**	−11.7*
Spleen	−11.5	+37.5*	+27.0
Testes	− 3.5	+14.1*	+ 3.9
Thymus gland	−35.1*	−12.4	−19.0
Residual carcass	−11.0*	− 7.0	− 5.6

†The results are expressed as % change from controls given no tannic acid, specifically as $((\bar{X}_D - \bar{X}_C) / \bar{X}_C) \times 100$ where $\bar{X}_D$ is the mean weight in g. of the drug-treated group, and $\bar{X}_C$ the mean in its control group. One asterisk indicates that the probability (P) that $\bar{X}_D - \bar{X}_C$ is zero, is 0.05 to 0.02; and two asterisks, that it is 0.01 or less.

TABLE II.—SHIFTS IN THE WATER LEVEL OF ORGANS AT AUTOPSY IN ANIMALS WHICH DIED AND IN SURVIVORS AT ONE FORTNIGHT AND AT ONE MONTH AFTER DRUG ADMINISTRATION†

Organ	*At death*	*Fortnight survivors*	*Month survivors*
Adrenal glands	+30.6**	−46.7**	+13.3
Brain	− 0.8	− 2.5	+ 0.3
Gastrointestinal tract:			
Cardiac stomach	+18.6**	− 1.2	+ 0.3
Pyloric stomach	+21.1**	+ 0.6	+ 3.0
Small bowel	+11.4*	− 3.8	+ 7.1
Cecum	+13.7*	− 1.0	− 6.5
Colon	− 3.6	+ 5.9	+ 4.6
Heart	+ 9.5	+ 1.2	− 3.6
Kidneys	+ 3.7	+ 0.9	+ 1.8
Liver	+13.1**	+ 8.2*	+ 4.9
Lungs	− 8.1**	− 3.0	+ 1.1
Muscle (abdomen wall)	− 2.7	+ 5.8	+ 4.3
Salivary glands (submaxillary)	−14.0**	+ 1.5	+10.6
Skin	+ 7.0	− 6.8	+11.8
Spleen	+ 0.3	+ 3.2	+ 5.1
Testes	− 6.6**	+ 0.8	+ 2.7
Thymus gland	− 3.0	− 4.0	− 2.3
Residual carcass	− 5.2	+ 5.0	+ 0.5

†Water levels were measured as g. water per 100 g. dry weight of tissue. The results are expressed as % change from controls given no tannic acid, specifically as $((\bar{X}_d - \bar{X}_c) / \bar{X}_c)$ x 100 where $\bar{X}_d$ is the mean in the drug-treated group and $\bar{X}_c$ in its control group. One asterisk indicates that the probability (P) that $\bar{X}_d - \bar{X}_c$ is zero, is 0.05 to 0.02; and two asterisks, that it is 0.01 or less.

47.2 ml. per kg. body weight versus 5.0 ml. per kg. in the controls. The excretion of protein, calculated as mg. per kg. body weight per 24 hours, increased from a normal average of 4.3 ± 2.1 mg. per kg. in the controls, but the increase was not dose-dependent over the dosage range studied. Urinary pH significantly increased from a control average of 6.5 ± 0.4 and the increase was dose-dependent during day 2. There were no significant changes in urinary glucose or in any of the recorded parameters in control rats given no tannic acid.

When death occurred within six hours from doses of 4.5 to 8.0 g. per kg., the common premortem signs were prostration, cyanosis, diarrhea, pallor, tremors, and convulsions followed by death due to respiratory failure. When death was delayed two to five days, it was preceded by a marked decrease in food and water intake, loss of body weight, hypothermia, pallor, cyanosis and, when observed, was due to respiratory failure sometimes preceded by slight convulsive tremors.

At autopsy there was found a significant loss of fresh weight in the intestines, kidney, liver, skin, thymus gland and residual carcass, and an increase in weight of the adrenal glands (Table I). Shifts in fresh weight were accompanied by significantly increased water levels in adrenals, most parts of the gastrointestinal tract and liver and significantly decreased levels in lungs, salivary glands and testes (Table II).

Histologically, oral administration of tannic acid produced a temporary fulminating gastroenteritis. There was marked capillary and venous congestion of the lamina propria and submucosa with capillary hemorrhages. The tips of the gastric glands and of the villi were lysed and there were areas of destruction of the normally resistant stratified squamous epithelium of the cardiac stomach. Peyer's patches stood out on gross observation as dark greyish-red areas due to marked vascular congestion seen microscopically. The gastrointestinal tract recovered quickly and the inflammatory reaction was almost gone at 48 hours and completely gone at 72 hours, leaving normal-appearing tissues with some hypertrophy of lymphocytic nodules. The gastroenteritis, therefore, could not have been a primary cause of death after the first day.

Development of hepatic necrosis reached its peak during the second and subsequent days. It began in the first 24 hours with the appearance of pale-stained, swollen, centrilobular hepatic cells and portal vein congestion. The nuclei of the hepatic and von Kupffer cells then became swollen and vacuoles appeared in the cytoplasm. At 48 to 72 hours the cytoplasm and then the nuclei of the hepatic cells underwent granular necrosis, with hemorrhage from the sinusoids into necrosed areas and complete or almost complete loss of hepatic microscopic structure. Granulocytes and monocytes, which appeared in blood in large numbers, invaded the necrosed areas. In some animals in which death was delayed to the fourth day there appeared to be a degree of fibrosis about the central vein, with partial occlusion of the lumen.

Nephritis appeared at the same time as the hepatic necrosis. It began at 24 hours as marked vascular congestion, especially of the glomerular tuft and loop region. This was accompanied by

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edema of the proximal and distal tubules and some regurgitation of tubular cells into the subcapsular space. By 48 hours Bowman's capsule had swollen and appeared to be fusing with the adjacent, now relatively avascular, glomerulus against which it was compressed by markedly swollen tubular tissue. In other areas there appeared tubular vacuolations and necrosis, and in still other areas nephrons appeared relatively normal. In some parts of the kidney, regions of capillary hemorrhage and cell infiltration were seen in the interstitial tissue, suggestive of early interstitial fibrosis.

The spleen was initially contracted and considerable debris appeared in the pulp cells. By the third day there was considerable hyperplasia of the white pulp and cords of Billroth. At the same time, hyperplasia and hypertrophy occurred in the adrenal cortex, especially in the zona fasciculata, and atrophy of the thymus, as indicated by a considerable loss of thymocytes.

For the most part the lungs were little affected by the intoxication. The lung parenchyma generally appeared somewhat hypovascular, although areas of congestion and edema were occasionally seen. The heart, skeletal muscle, pancreas, salivary glands, brain and skin appeared normal.

A curious finding was that the tannic acid seemed to have stimulated spermatogenesis in animals which were autopsied at 48 to 72 hours. In these animals the interstitial tissue of the testes was hyperemic and almost all of the seminiferous tubules showed active mitoses in spermatogenic cells, many spermatids and sperm. It may be noted in Table I that the weight of the testes was significantly augmented at two weeks in survivors.

At the same time, fortnight survivors had recovered much of the early loss of organ weight, the adrenals had returned to the normal weight range, and the spleen and testes were enlarged. At one month (Table I) the fresh weight of organs had returned to the normal range except that of the adrenal glands, pyloric stomach and skin, which were subnormal. At one month, body weight was within the normal range and the animals appeared normal on casual inspection. As shown in Table II, water levels of all tissues were within normal limits at one month. No histological examination was made upon the tissues of survivors.

DISCUSSION

Tannic acids are produced in plants from low-molecular-weight polyphenols exposed to oxidative condensation as a result of, for example, tissue injury, and they apparently serve to protect the plant from potential infection by tanning the invading viruses and fungi.[13] The complex chemical and physical properties of tannic acids have been reviewed by White.[14] Medicinal tannic acid of the British Pharmacopoeia is an extract containing various polyphenols which, presumably, could vary from batch to batch, since chemical composition is not specified. For this reason a chemically pure tannic acid, which could be termed 3-galloyl gallic acid, was used as a standard in the project described above. It will be recognized that the toxicity of other tannic acids found in different batches of medicinal tannic acids could vary from that of 3-galloyl gallic acid.

Tannic acid is readily absorbed from the gastrointestinal tract, peak blood levels being reached in about three hours,[15] and the metabolites are excreted in the urine.[16] Normal urine contains some of these metabolites, presumably derived from tannins in tea, coffee, and other plant extracts such as certain wines.[15]

Various plant extracts containing tannins have been used for centuries in the treatment of diarrhea and as astringents, antiseptics, and styptics on the skin and mucous membranes.[17] Astringent action is the pharmacological basis for the use of tannic acid in the local therapy of burns and as an adjuvant in the diagnostic barium sulfate enema.

Ancient use of tannin extracts revealed that large doses taken by mouth would produce an irritant gastroenteritis but the toxic dose was much higher than that of metallic astringents and tannins were considered relatively safe for oral use as antidiarrheics. Actually, the oral LD_{50} of the tannic acid used in the project reported above, namely 2.26 ± 0.083 g. per kg. body weight, is not much lower than that of sodium chloride, which was found in this laboratory to be 3.75 ± 0.043 g. per kg. in identical experiments on albino rats.[18] In rabbits, the LD_{50} of tannic acid given intragastrically has been reported as 5.0 g. per kg.[19] The preliminary conclusion from work now in progress in this laboratory[6, 7] is that tannic acid may be found to be considerably more toxic when given per rectum to albino rats. The preliminary explanation appears to be that when the drug is given per rectum it is not diluted by glandular secretions to the same extent as when it is given intragastrically. When the concentrated tannic acid is then permitted to act upon the colonic glands for several hours, the lining of the colon becomes necrotic. Absorption thus begins to approximate that from subcutaneous administration, by which route the lethal dose of tannic acid has been reported to be from some 135[9] to some 250[20] mg. per kg.

In the present project, the interval to death following oral administration of an LD_{50} of tannic acid was slightly less than that reported in rats following subcutaneous injection of an LD_{50}.[20] The results from oral administration to dogs are complicated by vomiting of the administered drug, but when the drug is retained death has been reported at from five hours to four days.[15]

The clinical signs of tannic acid intoxication observed in the present study included drowsiness, pallor, cyanosis, anorexia, diuresis, loss of weight, diarrhea, albuminuria and alkalinuria. Death was due to respiratory failure preceded by convulsions

or hypothermic prostration. In patients given tannic acid—barium sulfate enemas there have been reported drowsiness,[1, 2] prostration,[1, 2] anorexia,[1, 2] and pallor.[2] In animals given large doses of tannic acid there have been reported slow respiration,[9] hypothermia,[9] anorexia,[8] and loss of body weight.[8]

Pathologically, tannic acid intoxication was found in this study to be associated with a temporary acute gastroenteritis followed by nephritis and hepatic necrosis and was accompanied by hyperplasia of the spleen and adrenal cortex, atrophy of the thymus gland, and loss of weight and edema in many organs. Tannic acid poisoning in man has been found in association with gastric and duodenal ulcers, nephritis, and adrenal hemorrhage.[21] Hypertrophy of the adrenal glands and atrophy of the thymus have been reported in rats.[22]

Hepatic centrilobular cloudy swelling progressing to generalized necrosis has been previously reported in man,[21, 23] in rabbits and rats given tannin parenterally,[24] and in dogs, with delayed death following tannic acid given orally.[15] Long-continued administration of tannic acid can produce hepatic cirrhosis and tumours.[25, 26] Evidence of a temporary stimulation of growth in the spleen and testes, found in the present study, has not been previously reported.

SUMMARY

The LD_{50} ± S.E. of a tannic acid (3-galloyl gallic acid) administered by intragastric tube to albino rats with an empty stomach was found to be 2.26 ± 0.083 g. per kg. body weight. The interval from administration to death varied inversely with the dosage and averaged 38 hours at the LD_{50}. The clinical signs of intoxication were drowsiness, pallor, temporary diarrhea, cyanosis, anorexia, loss of body weight, diuresis, albuminuria and alkalinuria. Early deaths were due to respiratory failure following convulsive movements. Late deaths were due to respiratory failure following hypothermic cachexia. At autopsy there were significant loss of weight and gain in water content of many organs. There was a temporary acute gastroenteritis followed by gradual development of hepatic necrosis and nephritis, accompanied by hyperplasia of the spleen and adrenal cortex, augmented spermatogenesis and thymic atrophy. The lungs, heart, skeletal muscle, pancreas, salivary glands, brain and skin appeared normal. Recovery was accompanied by a temporary increase in weight of the spleen and testes at two weeks and persistent loss of weight in adrenal glands, pyloric stomach and skin at one month, at which time, however, water levels were normal in all organs. Oral administration of tannic acid, therefore, produced an early convulsive or late cachectic death, associated with hepatitis, nephritis and temporary acute gastroenteritis, and accompanied by loss of weight, edema and abnormal changes in many organs. Recovery was more or less complete in survivors at one month.

REFERENCES

1. LUCKE, H. H., HODGE, K. E. AND PATT, N. L.: *Canad. Med. Ass. J.*, 89: 1111, 1963.
2. MCALISTER, W. H. *et al.*: *Radiology*, 80: 765, 1963.
3. United States. Department of Health, Education and Welfare, Food and Drug Administration: Docket No. FDC-D-80, Federal Register, Superintendent of Documents, Government Printing Office, Washington, D.C., March 31, 1964.
4. THOMAS, S. F.: *Amer. J. Roentgen.*, 89: 889, 1963.
5. Editorial: *J. Canad. Ass. Radiol.*, 15: 2, 1964.
6. BOYD, E. M. AND SINGH, J.: Unpublished data.
7. BOYD, E. M. AND JARZYLO, S.: Unpublished data.
8. HANDLER, P. AND BAKER, R. D.: *Science*, 99: 393, 1944.
9. ROBINSON, H. J. AND GRAESSLE, O. E.: *J. Pharmacol. Exp. Ther.*, 77: 63, 1943.
10. BOYD, E. M. AND SHANAS, M. N.: *Canad. Med. Ass. J.*, 89: 171, 1963.
11. BOYD, E. M. AND KNIGHT, L. M.: *Toxic. Appl. Pharmacol.*, 5: 119, 1963.
12. CROXTON, F. E.: Elementary statistics with applications in medicine, Prentice-Hall, Inc., New York, 1953.
13. WHITE, T.: *J. Sci. Food Agric.*, 8: 377, 1957.
14. *Idem*: Chemistry of vegetable tannins, *In*: The chemistry and technology of leather, vol. 2, edited by F. O'Flaherty *et al.*, Reinhold Publishing Corporation, New York, 1958, p. 98.
15. KORPÁSSY, B., HORVAI, R. AND KOLTAY, M.: *Arch. Int. Pharmacodyn.*, 88: 368, 1951.
16. TOMPSETT, S. L.: *J. Pharm. Pharmacol.*, 11: 32, 1959.
17. BOYD, E. M.: Drugs acting on mucous membranes and skin. *In*: Pharmacology in medicine: a collaborative textbook, 2nd ed., edited by V. A. Drill, Blakiston Company, New York, 1958, p. 685.
18. BOYD, E. M. AND SHANAS, M. N.: *Arch. Int. Pharmacodyn.*, 144: 86, 1963.
19. DOLLAHITE, J. W., PIGEON, R. F. AND CAMP, B. J.: *Amer. J. Vet. Res.*, 23: 1264, 1962.
20. KORPÁSSY, B., KOVÁCS, K. AND SZTANOJEVITS, A.: *Acta Physiol. Acad. Sci. Hung.*, 3: 233, 1952.
21. ERB, I. H., MORGAN, E. M. AND FARMER, A. W.: *Ann. Surg.*, 117: 234, 1943.
22. KORPÁSSY, B., TÖRÖK, J. AND KOVÁCS, K.: *Acta Physiol. Acad. Sci. Hung.*, 1: 113, 1950.
23. GILLMAN, J. AND GILLMAN, T.: *S. Afr. J. Med. Sci.*, 13: 169, 1948.
24. KORPÁSSY, B.: *Schweiz. Z. Path.*, 12: 13, 1949.
25. KORPÁSSY, B. AND MOSONYI, M.: *Brit. J. Cancer*, 4: 411, 1950.
26. KORPÁSSY, B.: *Cancer Res.*, 19: 501, 1959.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

APPENDICULAR OBSTRUCTION

One of the puzzling features of acute appendicitis has always been the extraordinary variability in the nature and severity of the early symptoms. An interesting contribution on the pathogenesis of the disease, and one which may be of considerable clinical importance, has been made by Mr. D. P. D. Wilkie, of the Edinburgh Royal Infirmary, in a paper published in the *British Medical Journal* of December 5. While others have laid stress on the obstructive factor in appendicitis, he maintains that there are two clinical entities to be clearly differentiated, primary inflammation and primary obstruction. "If we set out by recognizing two definite types of acute disease of the appendix—namely, acute inflammation and acute obstruction—then not only does the understanding and the teaching of the symptomatology of acute appendicular disease become much simplified, but the early diagnosis of such disease becomes inevitably more confident and more correct." The destructive features of acute appendicular obstruction as contrasted with primary inflammation are, briefly, the great severity of the pain, the suddenness of its onset, and especially the absence of disturbance of the pulse and temperature during the initial stages. Vomiting is usually but not always present. The commonest causes underlying the obstruction are fibrous stenosis, resulting often from a previous appendicitis, and acute kinking by an abnormal band or fold, congenital or acquired. The immediate cause of the acute symptoms is the access of fæcal matter to the distal portion of the appendix beyond such a constriction.—Editorial, *Canad. Med. Ass. J.*, 5: 50, 1915.